

35 USC § 112

The Examiner has objected to the phrase "such as" in Claims 27, 34, and 40, under 35 U.S.C. §112, second paragraph, as allegedly rendering the claims indefinite. Applicants have amended claims 27 and 34 to delete the phrase objected to by the Examiner. Claim 40 has been deleted.

The Examiner has rejected Claims 35-40 under 35 U.S.C. §112, first paragraph. In order to expedite examination of this application, applicants have deleted Claims 35-40, rendering the rejection moot. Applicants reserve the right to introduce these claims into a later filed application.

35 USC § 102

Applicants are not sure whether a rejection under 35 U.S.C. §102 has been raised against claims 28 and 29. Although a partial rejection appears in the Office Action (page 7), the rejection does not identify any specific prior art over which the claims are allegedly anticipated.

35 USC § 103

Claims 22-29 and 31-34 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Skarnes in view of the combination of Ghattas et al. and Tsukiyama-Kohara et al. The Examiner acknowledges that Skarnes does not teach the incorporation of an IRES element into a gene trap vector, yet alleges it would have been obvious to one of ordinary skill in the art to construct a gene trap vector that combined the teaching of Skarnes with that of Ghattas et al. or Tsukiyama-Kohara et al. so as to introduce an IRES into a gene trap vector.

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Applicants respectfully disagree with this analysis and assert that, not only has the Examiner failed to make a *prima facie* case of obviousness, but also that the gene trap vector as claimed would not have been obvious in light of the cited prior art.

Of the three references cited by the Examiner, only Skarnes describes random gene trap vectors. Ghattas et al. or Tsukiyama-Kohara et al are purportedly relevant for their reference to IRES elements and uses of IRES elements in initiation of translation of coding sequences. As an initial matter, it should be noted that neither Ghattas et al. nor Tsukiyama-Kohara et al. suggests that an IRES should or even could be used in a random gene trap vector.

More importantly, however, while it is generally known that an IRES can be used in initiate mRNA translation, Skarnes does not mention or describe the use of IRES or identify any difficulties in initiation of translation in gene trap vectors. Hence, there is no suggestion found in Skarnes to modify the disclosed gene trap vector so as to alter the mechanism of initiation of translation. In addition, while reading frame limitations of the Skarnes type vectors were known at the time, Skarnes elected to address this problem by generating a mixture of three different gene trap vectors which initiate translation in three different reading frames but are otherwise identical. It is therefore clear that Skarnes already had a solution to this problem and thus, does not suggest a reason to address the problem in any other manner.

Furthermore, the gene trap vectors of Skarnes are used to determine information about the activity of particular genes during embryogenesis. (Abstract, last sentence, top left side of page 287.) See, also, page 827, right column, middle paragraph, last sentence, where Skarnes states that using the target gene's own translation initiation

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signal may ensure a more accurate representation of gene expression pattern of the gene that has been trapped using the gene trap vector. This is a clear teaching **against** the use of anything within the gene trap vector that would alter the initiation of translation. (Note also, in this regard, the legend to Figure 1, on page 828 where it is stated that the translation control of the reporter is present on the endogenous gene – see the “ATG” marked in gene X in Figure 1a.)

In order to establish a *prima facie* case of obviousness, the Examiner must set forth some objective reason to combine the teachings of the cited references. The mere fact that references **can** be combined does not render the resultant combination obvious in the absence of suggestion of the desirability of the combination. See, e.g., *In re Geiger*, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

As noted by the Federal Circuit “[i]t is impermissible to use the claimed invention as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is rendered obvious.” *In re Fritsch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). It is the duty of the Examiner to explain why the combination of the cited teachings is proper when, as here, the motivation to combine the teachings of the references is not apparent. *Ex parte Skinner*, 2 U.S.P.Q.2d 1788 (Bd. Pat. App. & Inter. 1986). This duty is not satisfied by the mere fact that the prior art references relied upon teach that all aspects of the claimed invention were individually known in the art and thus **can** be combined or modified. See *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993); *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Thus, the Examiner has not made a proper *prima facie* case of obviousness against claims 22-29 and 31-34, and the rejection should be withdrawn.

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Moreover, the Examiner has overlooked the significant differences between the cited art and the claimed invention. For example, Skarnes recounts how gene trap vectors generate fusion products and the fusion products are located in different sub-cellular compartments. (Page 827, right column, end of the penultimate paragraph.) This use of gene trap vectors to generate information about the sub-cellular localization of the gene products is a key element of Skarnes use of gene trap vectors and relies upon the use of the gene trap vector to generate a fusion product. In contrast, it is not possible for the IRES-containing gene trap vectors of the invention to generate fusion products, as the vectors are not being used to determine information about sub-cellular localization of the products.

A further distinction and significant advantage of the claimed invention over the cited art is the fact that in the Skarnes gene trap vectors, the heterologous gene sequence must be inserted in the correct reading frame. Therefore, the Skarnes method typically loses 2/3 of the insertions into active gene due to insertion out of the correct reading frame. The gene trap vectors of the present invention avoid this problem by providing their own translation initiation codon.

An additional disadvantage of the Skarnes method is that the fusion proteins generated often are non-functional because large upstream protein sequences arising from the endogenous gene in the fusion protein render the fusion protein inactive. The claimed invention advantageously avoids the production of these non-functional fusions.

Thus, in summary, applicants do not agree that the method and construct of the invention would have been obvious in light of Skarnes alone, or in combination with Ghattas et al. nor Tsukiyama-Kohara et al. Skarnes teaches the desirability of relying

upon the translation initiation signal from the endogenous gene. Skarnes teaches against modifications to the gene trap vector that would effect the level or pattern or any other aspect of the expression of the endogenous gene. Skarnes does not discuss any of the problems associated with his use of gene trap vectors. There is no motivation or even suggestion to incorporate the IRES elements of Ghattas et al. nor Tsukiyama-Kohara et al. into the gene trap vectors of Skarnes. Moreover, this combination would not result in a reasonable expectation of the success achieved by applicant's invention from those of skill in the art.

Applicants' invention, in contrast to any combination of the cited art, inserts a IRES element, providing its own translation initiation codon and generating expression of heterologous gene coding sequences that are not the fusion proteins produced using the method of Skarnes. The claimed invention provides a number of advantages compared with the method and construct of Skarnes. Therefore, the invention would not have been obvious over the cited prior art and the Examiner is asked to withdraw the rejection under this heading.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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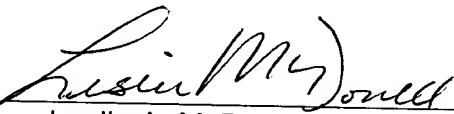
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Applicants believe that any extension of time required to file this Amendment and Response is accounted for by the accompanying Petition for Extension under 37 C.F.R. 1.136(a). However, if applicants are in error, please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 06-0916.

Respectfully submitted,

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